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Genetics of Nonsyndromic Recessively Inherited Moderate to Severe and Progressive Deafness in Humans

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1. Introduction

Nonsyndromic deafness in humans involves hearing loss as the only presenting feature in contrast to syndromes in which hearing loss is accompanied by other abnormalities. The majority of nonsyndromic deafness is recessively inherited which involves mutations of both alleles of a gene.

Deafness is a sensory impairment which results in a partial or total loss in reception of sound. The intensity of sound can be measured in decibels (dB). It is usual to assess hearing thresholds at frequencies of 0.25, 0.5, 1, 2, 4 and 8 KHz. Sounds of each frequency are presented at different intensities to a subject and the response is recorded graphically as an audiogram. A loss in hearing is indicated if the threshold for perception of sound for any frequency is elevated by 10 dB or greater as compared to the defined standard value for each frequency. Like visual foveae, organisms also have acoustic foveae, in which a certain frequency occupies greater space and is resolved more than other frequencies. In humans, the frequencies of 2 to 4 KHz are finely resolved. The frequencies of 0.5-2 KHz are the most important for hearing conversations. Therefore, individuals can have usable hearing if deafness does not impair these frequencies to a profound degree. A hearing loss of >91 dB constitutes profound deafness while those between 41 to 90 dB are defined as moderate (41-55 dB), moderate to severe (56-70 dB) or severe hearing loss (71-90 dB), respectively. Progressive deafness involves a gradual loss in the ability to hear over time.

The genetics and biology of moderate to severe and progressive hearing loss in humans has been understudied. More than 65 loci have been mapped for nonsyndromic recessively inherited deafness. Notably, mutations of only some of these genes are associated with stable moderate to severe hearing loss (Chishti et al., 2009; Naz et al., 2003; Villamar et al., 1999; Zwaenepoel et al., 2002). The past few years have revealed mutations in more than 10 genes and loci which can cause variable degrees of hearing loss or progressive deafness in humans. Additionally, the observation of intra- and inter- familial variability in the degree of deafness associated with identical mutations in a few genes has also implicated

a role for specific additional epistatic interactions which can modify the hearing loss in some instances.

2. Molecular genetics

Most individuals with inherited hearing loss suffer from profound deafness. It is hypothesized that the degree of hearing loss is profound when mutations affect genes which cause hair cell loss while it may be less severe or progressive in nature when mutations disrupt genes which affect hair cell function or that of the tectorial membrane (Grillet et al., 2009). In other instances, presence of missense or nonsense mutations in the same gene have been associated with variability in degree of hearing loss (Pennings et al., 2004). Additionally, some mutations creating new cryptic splice sites within genes have also been associated with intra-familial variability of hearing loss (Lopez-Bigas et al., 1999). However, in some instances there are no genotype-phenotype correlations. For example individuals who are homozygous for the c.35delG mutation in *GJB2* have phenotypes ranging from congenital and profound to early onset and mild hearing loss (Denoyelle et al., 1997; Snoeckx et al., 2005). There are a few other reports of identical mutations in the same gene in different subjects causing a significantly dissimilar hearing loss. This is illustrated by individuals with mutations in *CDH23*, *CLDN14* or *TRIC*. Individuals who are homozygous for identical mutations in *CDH23*, *CLDN14* or *TRIC* exhibit different degrees of hearing loss (Bashir, Fatima & Naz, 2010b; Riazuddin et al., 2006; Schultz et al., 2005).

Less severe degree of hearing loss may also result when mutations create hypomorphic alleles or affect particular domains of proteins. For example, a hypomorphic allele is hypothesized to be responsible for the moderate to profound hearing loss in affected individuals at the *DFNB73* locus (Riazuddin et al., 2009). It has also been shown that mutations that specifically disrupt the long isofrom of MYO15A cause less severe hearing loss in contrast to mutations which disrupt function of both isoforms (Bashir et al., in press, Cengiz et al., 2010; Nal et al., 2010).

Intra- or inter- familal phenotypic variability is also observed due to progression of hearing loss (*DFNB7*, *DFNB8*, *DFNB25*, *DFNB30*, *DFNB59, DFNB72/95, DFNB77, DFNB79*, *DFNB84* and *DFNB91*) (Charizopoulou et al., 2011; de Heer et al., 2011; Ebermann et al., 2007b; Grillet et al., 2009; Li et al., 2010; Rehman et al., 2011; Schraders et al., 2010a; Schraders et al., 2010b; Sirmaci et al., 2010; Walsh et al., 2002; Weegerink et al., 2011). Younger individuals with mutations in *BSND* (*DFNB73*) also have a less severe degree of hearing loss which suggests a progressive nature of their hearing loss (Riazuddin et al., 2009). Other loci for which hearing loss is reported as less than profound are based on data from single families and the causative genes are unknown (*DFNB32*, *DFNB33*, *DFNB71, DFNB89, DFNB93*) (Basit et al., 2011; Belguith et al., 2009; Chishti et al., 2009; Masmoudi et al., 2003; Medlej-Hashim et al., 2002; Mustapha et al., 1998; Tabatabaiefar et al., 2011). For some deafness loci the degree of hearing loss was reported to be moderate to severe or severe in degree, but audiograms were not provided (*DFNB13*, *DFNB22, DFNB32*, *DFNB33* and *DFNB89*) (Basit et al., 2011; Belguith et al., 2009; Masmoudi et al., 2004; Masmoudi et al., 2003; Zwaenepoel et al., 2002). The known instances in which the degree of hearing loss is less than profound or can progress to different degrees are summarized in Table 1.

LOCUS	GENE	PHENOTYPE	REFERENCE
DFNB1	*GJB2*	Mild to profound HL, No genotype-phenotype correlation	(Snoeckx et al., 2005)
*DFNB2**	*MYO7A*	A missense mutations may cause a less severe degree of HL	(Hildebrand et al., 2010)
DFNB3	*MYO15A*	Mutations affecting N-terminal extension domain cause less severe degree of HL	(Cengiz et al., 2010; Nal et al., 2007)
DFNB4	*SLC26A4*	Splice site and some missesnse mutations cause less severe degree of HL which may be progressive	(Kitamura et al., 2000; Lopez-Bigas et al., 1999; Luxon et al., 2003)
DFNB7	*TMC1*	Progressive HL in one family	(de Heer et al., 2011)
DFNB8	*TMPRSS3*	Hypomorphic alleles cause progressive HL	(Hutchin et al., 2005; Scott et al., 2001; Veske et al., 1996; Weegerink et al., 2011)
DFNB12	*CDH23*	Compound heterozygous mutations may cause progressive HL	(Astuto et al., 2002)
DFNB13	Unknown	Progressive or Severe HL (No audiograms provided)	(Masmoudi et al., 2004; Mustapha et al., 1998)
DFNB16	*STRC*	Moderate to severe HL (One audiogram provided)	(Villamar et al., 1999)
DFNB20	Unknown	Moderate to profound HL, progressive inferred	(Moynihan et al., 1999)
DFNB21	*TECTA*	Moderate to severe HL (Flat or U-shaped audiograms)	(Meyer et al., 2007; Naz et al., 2003)
DFNB22	*OTOA*	Moderate to severe HL (No audiogram provided)	(Zwaenepoel et al., 2002)
DFNB25	*GRXCR1*	Progressive HL	(Schraders et al., 2010a)
DFNB29	*CLDN14*	Moderate to profound HL, No genotype-phenotype correlation	(Bashir et al., 2010b)
DFNB30	*MYO3A*	Progressive HL	(Walsh et al., 2002)
DFNB32	Unknown	Severe HL (No audiograms provided)	(Masmoudi et al., 2003)
DFNB33	Unknown	Severe HL (No audiograms provided)	(Belguith et al., 2009; Medlej-Hashim et al., 2002)
DFNB42	*ILDR1*	Moderate to profound HL	(Aslam et al., 2005; Borck et al., 2011b)
DFNB49	*TRIC*	Moderately severe to profound HL, No genotype-phenotype correlation	(Riazuddin et al., 2006)
DFNB59	*PJVK*	Progressive HL in two families	(Ebermann et al., 2007b)

LOCUS	GENE	PHENOTYPE	REFERENCE
DFNB71	Unknown	Severe HL (One audiogram provided)	(Chishti et al., 2009)
DFNB72/95	*GIPC3*	2 families with mild to severe HL, Individuals with a C terminal mutation have progressive HL	(Charizopoulou et al., 2011; Rehman et al., 2011)
DFNB73	*BSND*	Younger individuals have less severe degree of HL	(Riazuddin et al., 2009)
DFNB77	*LOXHD1*	Progressive HL in one family	(Grillet et al., 2009)
DFNB79	*TPRN*	Progressive HL in one family, Moderate to severe HL in another	(Li et al., 2010)
DFNB84	*PTPRQ*	Progressive HL or Moderate to severe HL	(Schraders et al., 2010a; Shahin et al., 2010a)
DFNB89	Unknown	Moderate to severe HL, no audiograms provided	(Basit et al., 2011)
DFNB91	*SERPINB6*	Progressive HL	(Sirmaci et al., 2010)
DFNB93	Unknown	Moderate to Severe HL	(Tabatabaiefar et al., 2011)

Table 1. List of nonsyndromic recessive deafness loci associated with less than profound deafness

The table lists autosomal nonsyndromic recessive deafness loci for which at least two individuals are reported to have a less severe hearing loss (<80 dB). HL, Hearing loss. * Only one patient has a dramatically less severe degree of hearing loss.

2.1a Genes involved in moderate to severe hearing loss

Three genes have been identified in which mutations exclusively cause recessively inherited moderate to severe hearing loss in humans. Interestingly, they are either part of the tectorial membrane, or are in direct contact with it. The tectorial membrane acts as the cochlear amplifier and results in gain in sound intensity by 30 dB. No progression has been documented for hearing loss due to mutations in the three genes, *STRC*, *TECTA* and *OTOA*, although some variability in degree of auditory thresholds is observed in affected individuals with identical mutations in these genes.

STRC (DFNB16)

Mutations in *STRC* encoding stereocilin are reported to cause mild to severe deafness in humans with an onset in childhood at 3-5years with increased involvement of high frequencies (Verpy et al., 2001; Villamar et al., 1999). Additionally, mice with a targeted deletion of *Strc* become progressively deaf by P60 (Verpy et al., 2008). The DPOAE cannot be recorded at P14 in $Strc^{-/-}$ mice though hearing thresholds are almost normal at that age. $Strc^{-/-}$ mice lack horizontal top connectors of outer hair cells' stereocilia. It is interesting to note that stereocilin may establish contact with tectorial membrane as inferred by lack of characteristic ring like staining of STRC from tallest row of outer hair cell stereocilia in $Tecta^{\Delta ENT/\Delta ENT}$ mice which have disrupted tectorial membranes due to loss of TECTA (Verpy et al., 2008).

TECTA (DFNB21)

Inactivating mutations of *TECTA* lead to moderate to severe recessively inherited hearing loss in humans which can be more severe in the mid frequencies leading to a flat or U shaped audiogram (Meyer et al., 2007; Naz et al., 2003). *TECTA* is the major protein of the tectorial membrane which lies over the organ of Corti within the cochlea. The tectorial membrane is in contact with the tallest stereocilia of the outer hair cells and acts as a cochlear amplifier which was elegantly shown in mice with a targeted mutation in *Tecta* (Legan et al., 2000). $Tecta^{\Delta ENT/\Delta ENT}$ mice have detached tectorial membranes and the noncollagenous matrix is missing. $Tecta^{\Delta ENT/\Delta ENT}$ mutants are 35 dB less sensitive to sound. However DPOAE can be elicited at high threshold sounds of 65 dB SPL in $Tecta^{\Delta ENT/\Delta ENT}$ mice (Lukashkin et al., 2004) though these are absent in humans with homozygous inactivating *TECTA* mutations (Naz et al. 2003, unpublished data).

OTOA (DFNB22)

Two Palestinian families have been reported in which the affected individuals had hearing loss due to deleterious mutations in the gene encoding otoancorin, *OTOA* (Shahin et al., 2010b; Zwaenepoel et al., 2002). The hearing loss was reported to be moderate to severe in one family while it was profound in the other. One of the families had a splice site mutation in *OTOA* (Zwaenepoel et al., 2002) while the second family with members affected with profound deafness had a complete deletion of the gene (Shahin et al., 2010b; Zwaenepoel et al., 2002). *OTOA* has sequence similarity to *STRC* (Jovine, Park & Wassarman, 2002) although its expression pattern is different. Both OTOA and STRC are predicted to be superhelical lectins which can bind the carbohydrate moieties of extracellular glycoproteins (Sathyanarayana et al., 2009). In mice, *Otoa* expression is restricted to specific regions between sites of attachment of tectorial membrane and underlying sensory epithelia.

2.1b Loci involved in moderate to severe or severe hearing loss

There are five chromosomal regions which have been implicated in genetics of moderate to severe hearing loss and the genes are currently unknown. Although *DFNB32* and *DFNB82* were mapped to overlapping regions on chromosome 1, the identification of *GPSM2* mutations for the latter (Walsh et al., 2010) excluded this as the causative gene for the former since it lies outside the linkage interval of *DFNB32* (Masmoudi et al., 2003).

DFNB32, DFNB33, DFNB71, DFNB89, DFNB93

Five loci for less severe hearing loss have been mapped to chromosomes 1p13.3-22.1, 10p11.23-q21.1, 8p22-21.3, 16q21-q23.2 and 11q12.3-13.3 respectively (Belguith et al., 2009; Chishti et al., 2009; Masmoudi et al., 2003; Tabatabaiefar et al., 2011). All loci have been described in single families except for *DFNB89* for which two families were reported. Deafness was described to be moderate to severe in degree in all affected individuals in these two families but no audiometric data was provided. Similarly, hearing loss is described as being severe in degree for families linked to both *DFNB32* and *DFNB33* without provision of audiometric data. Patients in families described for *DFNB71* and *DFNB93* have severe and moderate to severe hearing loss respectively as documented by 1 and 4 audiograms respectively. The identification of genes involved in pathogenesis due to mutations at these loci will shed light on their essential functions in the auditory pathways.

2.2 Genes involved in Intra- or inter- familial variability of hearing loss

GJB2 (DFNB1)

In the cochlea, gap junctions are proposed to maintain K^+ homeostasis by transporting K^+ away from the hair cells during auditory transduction (Kikuchi et al., 1995). *GJB2* encodes connexin 26 which oligomerizes to form a connexon (a hemichannel) which binds to a connexon from adjacent cell to form a functional gap junction in many tissues including the inner ear. *GJB2* is expressed in the supporting cells and the stria vascularis in the cochlea. The important function of *GJB2* in normal hearing is shown by the large number of mutations which have been reported in this gene from most diverse human populations which cause deafness. Although most individuals who are homozygous for c.35delG mutation in *GJB2* have severe to profound deafness, many individuals with the identical mutation have a mild or a less severe hearing loss (Murgia et al., 1999). Additionally, patients who are compound heterozygous for one truncating mutation together with a missense mutation in *GJB2* usually have a less severe hearing impairment (Liu et al., 2005; Snoeckx et al., 2005).

MYO7A (DFNB2)

MYO7A encodes a protein classified as an unconventional myosin which plays a role in intracellular trafficking. Unconventional myosins are actin-activated motor proteins with structurally conserved heads important for movement along actin filaments. The tails are highly divergent and are presumed to interact with different macromolecular components in the cell. All mutations in *MYO7A* except one cause severe to profound deafness. However, an individual with a missense mutation affecting the motor domain of MYO7A had a dramatically reduced hearing loss as compared to all other cases with *MYO7A* mutations, including those in his own family (Hildebrand et al., 2010). The onset of deafness was delayed to seven years of age and the degree of hearing loss was moderate to severe at the age of 31.

MYO7A is present in cytoplasm of hair cells and in the stereocilia including the upper tip-link density (Grati & Kachar, 2011). Different mutations of *Myo7a* result in profound deafness in mice (Gibson et al., 1995). However, one missense mutation affecting the kinesin and MyTH4 domains of myosin 7a leads to a severe deafness phenotype in contrast to other mice with mutations in *Myo7a* (Mburu et al., 1997).

MYO15A (DFNB3)

Mutations in *MYO15A* are a significant cause of deafness in many world populations. All pathogenic mutations in *MYO15A* except three which are located in exon 2 cause profound deafness. The four mutations were identified in three Pakistani and one Turkish families and are associated with hearing loss which can range from moderate to severe or moderate to profound in degree (Bashir et al., in press, Cengiz et al., 2010; Nal et al., 2010). The mutations in alternatively spliced exon 2 affect the class 1 isoform of MYO15A which has a long N-terminal extension. The presence of residual hearing in affected individuals who have mutations in exon 2 of *MYO15A* is probably due to the availability of normally functioning short isoform of MYO15A which remains unaffected by the mutations in exon 2 (Nal et al., 2007).

MYO15A is a motor protein present in hair cells in a cap like structure at top of the stereocilia where it is known to interact with WHRN (Belyantseva et al., 2005). It is

interesting to note that mutations affecting the long isoform of WHRN (Ebermann et al., 2007a) also cause a less severe hearing loss in contrast to mutations which disrupt the short isoform (Mburu et al., 2003).

Currently, no corresponding mouse carrying a mutation affecting the long N terminal extension domain has been reported. However, in *shaker 2* mice, a missense mutation affects the motor domain of MYO15A and the mice are profoundly deaf (Probst et al., 1998) . The stereocilia are extremely short and this defect can be fully rescued by transfecting *shaker 2* hair cells with MYO15A isoform 2 (Belyantseva et al., 2005). No specific role is known for MYO15A isoform 1 and its function remains to be elucidated.

SLC26A4 (DFNB4/PDS)

SLC26A4 mutations may cause Pendred syndrome or non-syndromic deafness with enlarged vestibular aqueducts. Considerable residual hearing is present in some affected individuals who are homozygous for mutations creating new splice sites in *SLC26A4* (Lopez-Bigas et al., 1999; Naz, 2001). These two described mutations create splice sites a few nucleotides away from the canonical donor sites, and support the hypothesis that variable degree of hearing loss in *SLC26A4* linked families may indicate splice site mutations. Additionally, a few missense mutations of *SLC26A4* also cause a significantly less severe hearing loss (Kitamura et al., 2000). Some mutations of *SLC26A4* result in development of a progressive hearing loss (Luxon et al., 2003).

SlC26A4 or pendrin is expressed in endolymphatic duct and sac as well as in the external sulcus in the cochlea (Everett et al., 1999). SLC26A4 plays a significant role in the maintenance of the ionic balance within the inner ear and is involved in bicarbonate secretion (Wangemann et al., 2007). There are three different mouse mutants of *Slc26a4* which lack pendrin but none of them model the less severe hearing loss observed in humans (Dror et al., 2010; Everett et al., 2001; Lu et al., 2011). However, recently, transgenic mice with *Slc26a4* expression inducible by doxycycline on a background of mice lacking endogenous pendrin expression were generated. It was demonstrated that expression of pendrin at early embryonic stages of E0-E17.5 was necessary and sufficient to restore normal hearing in Tg[E];Tg[R];*Slc26a4*$^{\Delta/\Delta}$ mice (Choi et al., 2011). Ablating expression of *Slc26A4* at this critical time results in complete or partial hearing loss in these mice, recapitatulating the phenotypes documented for many patients with mutations in *SLC26A4* (Choi et al., 2011).

CLDN14 (DFNB29)

CLDN14 is an integral part of the tight junctions in the sensory epithelium within the inner ear. Only two mutations have been reported in this gene in four Pakistani families which cause hearing loss. The usual phenotype associated with the two mutations is severe to profound deafness (Wilcox et al., 2001). However members of one family with p.V85D mutation in *CLDN14* have hearing loss which varies from moderately severe to severe in degree (Bashir et al., 2010b). It is interesting to note that mice with a targeted deletion of *Cldn14* are profoundly deaf and no variability of hearing loss was observed in these mice (Ben-Yosef et al., 2003).

ILDR1 (DFNB42)

ILDR1 is a membrane protein with an Immunoglobulin-like extracellular domain, and has different motifs for interaction with other proteins. Additionally, soluble isoforms of ILDR1

also exist which may be involved in lipoprotein transport (Borck et al., 2011b). Hearing loss due to mutations of this gene varies from moderate to profound in different individuals while it is severe in degree for one family with a mutation affecting the start codon of *ILDR1* (Borck et al., 2011b). *Ildr1* is expressed in the developing mouse cochlea but the expression is low at birth. It increases gradually by P4 and P10. The pillar and Hensen cells have the highest expression of *Ildr1* while it can also be detected in other cells in organ of Corti including the hair cells (Borck et al., 2011b).

TRIC (DFNB49)

TRIC or *MARVELD2* encodes a tight junction protein with a ubiquitous expression in the epithelial junctions throughout the body tissues. In the inner ear, TRIC is specifically expressed in the tricellular junctions of sensory epithelia as well as those between supporting cells and the hair cells (Riazuddin et al., 2006). Affected individuals with identical mutations in *TRIC* show a wide range of variability in severity of deafness ranging from moderate to severe hearing loss to profound deafness (Chishti et al., 2008; Riazuddin et al., 2006). All mutations described in *TRIC* are predicted to produce truncated proteins and consequent inability to bind several scaffolding proteins.

2.3 Genes involved in Progressive Hearing Loss

There are a few genes mutations in which have been described to cause progressive loss in hearing (*MYO3A*, *LOXHD1*, *PTPRQ* and *SERPINB6*). Additionally, some mutations in genes which cause stable and profound deafness, for example *TMC1* and *TMPRSS3* also cause progressive hearing loss. Many different mutations have been described in *TMC1*, *TMPRSS3*, *GRXRC1*, *PJVK*, *GIPC3*, *TPRN* and *PTPRQ* in affected individuals from different countries. However, it is noteworthy that apart from *DFNB8* (*TMPRSS3*), *DFNB59* (*PJVK*)) and *DFNB84* (*PTPRQ*) only one family is reported to have progression of deafness for each locus. All other mutations in these genes have been described to cause stable, moderate to profound deafness. This could be due to either of two reasons; the hearing loss associated with other mutations in these genes may also be progressive (slow or rapid progression) and has not been documented since many patients undergo audiometry at the time of enrollment in a genetic study. Alternatively, some mutations affecting a gene may cause a progressive hearing loss due to the type of mutation as for example those in *TMPRSS3*. Identical mutations may also cause stable or progressive hearing loss depending on the genetic background of the individuals.

TMC1 (DFNB7)

Homozygous inactivating mutations in *TMC1* cause severe to profound prelingual hearing impairment at the *DFNB7* locus. However, a Dutch family with autosomal recessive hearing loss was reported in which affected individuals had a postlingual onset, progressive hearing loss due to a mutation near the donor splice site of intron 19 (c.1763+3A→G) in *TMC1* (de Heer et al., 2011). The hearing loss initially affected the high frequencies and by second decade of life the hearing loss progressed to profound degree. This was documented as a "corner audiogram". Both normally spliced and aberrantly spliced *TMC1* transcripts were detected in blood of the patients. The presence of some wild type protein may account for the late onset of deafness and residual hearing in the patients, or alternately, the truncated mutant protein may have residual function (de Heer et al., 2011).

TMC1 is a transmembrane protein present in hair cells and may be involved in intracellular protein trafficking. Additionally it is also proposed to play a role in differentiation of hair cells into functional auditory receptors. The *deafness* mice mutants carry a homozygous genomic deletion in *Tmc1* and are profoundly deaf (Kurima et al., 2002). Currently there is no mouse model which mimics the recessively inherited progressive hearing loss due to mutations in *Tmc1* though a model, *Beethoven* exists for dominant deafness *DFNA36* and the mice have a missense mutation in *Tmc1* (Vreugde et al., 2002).

TMPRSS3 (DFNB8)

The gene encoding serine protease, TMRSS3 is expressed in supporting cells, stria vasularis as well as in the spiral ganglion in the inner ear. Mutations in *TMPRSS3* are responsible for deafness at the *DFNB8* locus. Most mutations in *TMPRSS3* result in severe to profound deafness in many world populations. However there are many mutations in *TMPRSS3* causing less severe hearing loss which is progressive in nature. The first family with progression in hearing loss due to a *TMPRSS3* mutation was reported from Pakistan. Affected members in this family suffered from progressive deafness with onset of hearing loss in childhood and had a mutation at a splice acceptor site in intron 4 (Scott et al., 2001; Veske et al., 1996). This is predicted to create an alternative splice acceptor site which on use introduces a frameshift in the open reading frame of *TMPRSS3*. It is hypothesized that this mutation may allow limited normal splicing since the actual splice site remains unchanged. Thus some normal TMPRSS3 could be produced accounting for progressive hearing loss observed in the affected individuals.

There are other reports of mutations in *TMPRSS3* causing post-lingual progressive deafness in British, Turkish, German and Dutch families (Elbracht et al., 2007; Hutchin et al., 2005; Wattenhofer et al., 2005; Weegerink et al., 2011). One of the first studies reported a British family with two affected individuals who were homozygous for a missense mutation in *TMPRSS3* and suffered from moderate to severe hearing loss (Hutchin et al., 2005). A recent study involved 8 small nuclear families from Holland and affected individuals were compound heterozygous for different mutations of *TMPRSS3* including missense and frameshift mutations (Weegerink et al., 2011). The higher frequencies were affected first resulting in a distinctive "ski-slope" audiometric configuration followed by low frequency hearing loss resulting in a flat audiogram (Weegerink et al., 2011). It was hypothesized that some mutations in *TMPRSS3* result in creation of hypomorphic alleles accounting for the less severe loss in hearing and progression of deafness observed in affected individuals (Weegerink et al., 2011).

Tmprss3 was shown to be important for hearing in mice as well since mutants homozygous for a nonsense mutation in the gene suffer from deafness. The hair cells start to degenerate at P12 from basal to apical turn of the cochlea and the degeneration is complete by P14 (Fasquelle et al., 2011). However, no mouse model has been reported which mimics the progressive hearing loss as observed in humans.

CDH23 (DFNB12)

Most mutations of *CDH23* cause severe phenotypes of deafness or *USH1D*. However, a few missense mutations in *CDH23* when present together in compound heterozygosity are reported to cause moderate to severe hearing loss or severe to profound deafness which is

progressive in nature (Astuto et al., 2002). In two German siblings with deafness, the age of onset was also different, with onset of hearing loss at 4 and 6 years respectively. The degree of hearing loss was variable and there was asymmetric hearing loss in the older sibling.

In the inner ear, *CDH23* is expressed in the hair cells and Reissner's membrane. Mice lacking CDH23 are profoundly deaf and suffer from developmental defects of the stereocilia (Di Palma et al., 2001). In contrast, ENU induced *salsa* mutants have a recessively inherited missense mutation in *Cdh23* which affects the tip links of the stereocilia (Schwander et al., 2009). These mice have a progressive hearing loss which increases from severe in degree to profound deafness by three months of age as a consequence of gradual loss of tip links and eventual hair cell death (Schwander et al., 2009).

GRXCR1 (DFNB25)

Splice site mutations were identified in *GRXCR1* in two Dutch families while three missense and a nonsense mutation were identified in *GRXRC1* in families from Pakistan and Iran which segregated with hearing loss (Odeh et al., 2010; Schraders et al., 2010a). Two mutations create alternative splice sites within *GRXCR1* which on usage are predicted to create frameshifts in the open reading frame of the gene. The presence of alternatively spliced transcripts was demonstrated for one of the splice site mutations by an *in vivo* assay on lymphoblastoid cell lines derived from patients' blood.

The single affected individual in one of the Dutch families with a splice site mutation had a significantly milder phenotype of moderate to severe hearing loss which was not progressive in nature. Additionally, the hearing loss in affected members of another Dutch family and Pakistani families varied from moderate to profound in degree. The loss in hearing was progressive from moderate to profound in the Dutch family, while it was severe in the two families from Pakistan (Schraders et al., 2010a). The audiometric profile varied from flat to a slight U-shape and was down-sloping (Schraders et al., 2010a). Data was not provided about the audiometric profile of affected individuals in families from Iran, although hearing loss was reported to be severe to profound in degree (Odeh et al., 2010).

GRXCR1 is predicted to contain a GRX-like domain. These domains take part in reversible S-glutathionylation of proteins by which they are predicted to control activity or localization of the proteins. In the inner ear, *Grxcr1* is expressed in the hair cells and is localized along the lengths of stereocilia exhibiting a differential pattern in levels of expression in young and adult mice (Odeh et al., 2010). There are five mutant alleles of *Grxcr1* which cause profound deafness in the *pirouette* mice (Odeh et al., 2010). The absence of GRXCR1 results in formation of relatively short and thin stereocilia and cytocauds indicating actin abnormalities. This suggests that GRXCR1 plays an active role in development of actin architecture in the stereocilia (Beyer et al., 2000; Odeh et al., 2010).

MYO3A (DFNB30)

A class III myosin, *MYO3A* is required for normal hearing as shown by a single family originating from Iraq in which affected individuals had a progressive hearing loss with onset in second decade of life (Walsh et al., 2002). Interestingly, three different mutations were identified in this family which were either present in homozygosity or individuals were compound heterozygous for any of the mutations. The hearing loss first affected high

frequencies. By the age of 50 there was moderate hearing loss at low frequencies while the high and middle frequencies were severely affected. All individuals were equally affected by the sixth decade of life. The three mutations identified in *MYO3A* included a nonsense and two splice site mutations. Hearing loss was significantly worse in affected individuals homozygous for the nonsense mutation than those who were compound heterozygous for a nonsense and a splice site mutation.

MYO3A is present in the hair cells stereocilia at the tips in a characteristic pattern described as "thimble-like" (Schneider et al., 2006) with presence at the stereocilia tip and also extending further down into the shaft of the stereocilia. Mice created as models for *DFNB30* mimic the hearing loss phenotype observed in humans. *Myo3a*$^{KI/KI}$ mice have an engineered nonsense mutation in the gene and they exhibit a hearing loss which progresses from mild to moderate, and to moderate to severe between ages of 2.5 months to 13 months. More severe loss in hearing is observed for sounds of high frequencies. In *Myo3a*$^{KI/KI}$ mice, development of hair cells stereocilia is normal which is followed by a gradual loss of hair cells from basal to apical turn of the cochlea (Walsh et al., 2011). It is hypothesized that loss of MYO3A may result in failure of transport of essential components within stereocilia (Walsh et al., 2011). This affects signal transduction in the inner ear, leading to loss of function and ultimate degeneration of hair cells.

PJVK (DFNB59)

Mutations in *PJVK* cause hearing loss with or without auditory neuropathy. The hearing loss is severe to profound and stable in all individuals reported so far except in members of one Moroccan, one Iranian and three Arab families (Borck et al., 2011a; Ebermann et al., 2007b; Schwander et al., 2007). Three affected individuals in the Moroccan family had deafness with onset by age of 4 in one individual and congenital hearing loss was observed in the other two individuals. The loss in hearing is severe in degree in the former and profound in the latter two individuals. Audiometry performed over a period of three years revealed a progressive nature of hearing loss for all three affected individuals. Unlike other families with *PJVK* mutations which have missense mutations in the gene, this family had a frameshift mutation in exon 2 of the 7 exon gene and the mutation is predicted to severely truncate the protein. Hearing loss is also reported to be progressive in nature and moderate to profound in degree in a family from Iran with a frameshift mutation of *PJVK* but audiometric profiles were not provided (Schwander et al., 2007). Additionally, deafness due to a nonsense mutation in three Arab families is reported to cause stable moderate to severe hearing loss but no audiograms were provided (Borck et al., 2011a).

PJVK exhibits 32% identity and 54% similarity over a stretch of 250 amino acids to DFNA5 protein. It is expressed in the hair cells and spiral ganglion. Mice with a targeted knock-in missense mutation in *Pjvk*, *Dfnb59*$^{tm1Ugds/tm1Ugd}$ have a moderate to severe non-progressive hearing loss which is elevated at high frequencies (Delmaghani et al., 2006) unlike *sirtaki* mice which have a nonsense mutation in *Pjvk* (Schwander et al., 2007). The *sirtaki* mice have outer hair cell functional defects as apparent by absent DPOAE and also suffer from progressive deafness. No morphological defects are apparent in the ears of the *sirtaki* or knock-in mutant mice. It is hypothesized that that functional null allele of *Pjvk* inactivates protein function in both hair cells and neurons, while the missense mutation affect its function only in the neurons.

GIPC3 (DFNB72/15/95)

GIPC3 encodes a PDZ domain containing protein which is important in peripheral auditory signal transmission. Mutations in this gene cause both profound deafness and progressive hearing loss. In a small Dutch hearing loss followed a different course in the two affected siblings. In the oldest affected individual, the loss in hearing was 70 dB HL at 11 months which progressed to 110 dB HL by 12 years of age. The hearing loss in second individual was 80 dB HL at 3 months which seemed to be stable as it only progressed to 90 dB HL by age of 14 years. (Charizopoulou et al., 2011). The mutation in *GIPC3* identified in the Dutch family introduces a stop codon in exon 6 (p.W301X) truncating the C-terminal. It is hypothesized that since this mutation is in the last exon it will not cause nonsense mediated decay and will allow production of a mutant protein retaining some function.

GIPC3 mutations have also been reported in seven other large families from Pakistan which include one framsehift and and six missense mutations (Rehman et al., 2011). The younger affected individuals in these families (7 and 9 years old) had better hearing as compared to the older affected individuals (20 and 25 years old). However, information is not available as yet whether hearing loss in any of the affected individuals is stable or progressive.

A mutation affecting PDZ domain of GIPC3 has also been reported in mice which causes progressive hearing loss, *ahl5* (Charizopoulou et al., 2011). The mice have a moderate hearing loss at one month of age which progresses to profound in degree by 1 year of age. The higher frequencies are affected first with eventual involvement of all frequencies. DPOAE and the endocochlear potential are gradually affected as well. The stereocilia are defective and degenerate together with the spiral ganglion cells.

BSND (DFNB73)

BSND encodes barttin which is an essential subunit for two chloride channels. Heteromeric channels formed by barttin and the chloride channels play an important role in potassium recycling in the inner ear (Estevez et al., 2001). A missense mutation, p.I12Tof BSND segregates with hearing loss in three families from Pakistan while in a fourth family it is present with a nonsense mutation in compound heterozygosity (Riazuddin et al., 2009). The younger individuals have a less severe hearing loss as compared to the older affected individuals suggesting that *BSND* may be involved in aetiology of progressive deafness. Functional analysis of the p.I12T mutation of *BSND* in HEK293T cells have demonstrated that function of the channels is unaffected. However, the number of channels on the surface membrane is reduced which results in a decreased current amplitude (Riazuddin et al., 2009).

LOXHD1 (DFNB77)

The 15 PLAT (polycystin/lipoxygenase/a-toxin) domains encoding gene *LOXHD1* was found to be mutated in an Iranian family with postlingual onset of hearing loss at ages ranging from 7 to 8 years. Affected individuals in the family had preserved hearing at low frequencies in the beginning. The loss was mild to moderate at frequencies of 0.5 to 2 KHz. Hearing loss worsened during childhood and adolescence to moderate to severe at mid and high frequencies. All frequencies were affected eventually (Grillet et al., 2009). A nonsense mutation, p.R670X was identified which introduces a premature stop codon at the C-terminal end of f the fifth PLAT domain. This could either lead to a protein lacking 10 PLAT

domains or nonsense mediated decay of the transcript could lead to absence of LOXHD1. In contrast, the only other mutation reported in *LOXHD1* is a founder mutation, p.R1572X, in the Ashkenazi Jews and causes prelingual profound degree of deafness (Edvardson et al., 2011).

Normally LOXHD1 is present along the lengths of hair cell stereocilia plasma membrane while it cannot be detected at the tips of the stereocilia (Grillet et al., 2009). Interestingly, the hair cells bodies have no expression of *LOXHD1*. ENU induced *samba* mutants homozygous for a missense mutation in *Loxhd1* acquire hearing loss by 3 weeks of age and are completely deaf by eight weeks. The stereocilia develop normally. However, the hair cells have functional defects and DPOAE cannot be elicited from ears of *samba* mutants. Morphological defects are also observed in the inner ears of *samba* mutants with fused stereocilia and ruffled membranes at the apical cell surfaces. Additional degenerative changes are visible by post natal day 90 which include hair cell loss (Grillet et al., 2009).

TPRN (DFNB79)

Mutations of *TPRN* cause different degrees of hearing loss in humans. In a Dutch family, hearing loss is documented as moderate to severe in degree till 11 years of age and by 15 years it progresses to profound deafness (Li et al., 2010). In contrast, hearing loss in a Moroccan family is severe in degree even in the third decade of life (Li et al., 2010). Affected members of the Dutch family had a nonsense mutation in exon 1 of *TPRN* while the affected individuals in the Moroccan family were homozygous for a frameshift mutation in exon 1. It is interesting to note that the same frameshift mutation as observed in the Moroccan family was also identified in a Pakistani family. However, individuals in this family had profound degree of deafness (Khan et al., 2009; Rehman et al., 2010).

TPRN is present in the supporting cells as well as at the base of hair cells' stereocilia in the organ of Corti at the taper region of each stereocilium just above the cuticular plate (Rehman et al., 2010).

PTPRQ (DFNB84)

Congenital hearing loss which has been shown to be progressive in nature is associated with mutations in *PTPRQ*, a gene which encodes a phosphatase specific for phoshatidyl inositol, $PI(4,5)_{P2}$ (Schraders et al., 2010b; Seifert et al., 2003). $PI(4,5)_{P2}$ plays an important part in actin remodeling. Hearing loss due to mutations *PTPRQ* is severest in a Dutch family with a p.Y497X mutation and hearing loss was self reported to have progressed to profound by the third to fourth decade of life. However in affected individuals of a Moroccan family, a p.R457G mutation in PTPRQ caused a less severe loss in hearing. The loss in hearing was moderate which had deteriorated with age (Schraders et al., 2010b). Otoacoustic emissions were normal at the age of 13 months. The 1 to 2 KHz frequencies seemed to be more affected comparable to that observed in members of a Palestinian family with moderate to severe hearing loss also with a mutation of *PTPRQ* (Shahin et al., 2010a). In the Palestinian family, there were four affected individuals with considerable variation of hearing loss. A nonsense mutation, p.Q429X, was observed in *PTPRQ* for this family (Shahin et al., 2010a). Data is not available about progression of deafness in the Palestinian family.

Ptprq is transiently expressed over a period of first three weeks in mouse hair cells at the basal turn of the cochlea (Goodyear et al., 2003). MYO6 plays a role in localization of PTPRQ

in plasma membranes (Sakaguchi et al., 2008). PTPRQ has been shown to be required for formation of shaft connectors and the taper of the stereocilia (Goodyear et al., 2003; Sakaguchi et al., 2008). Two transgenic mouse mutants, *Ptprq-TM-KO* and *Ptprq-CAT-KO* were generated in which the alleles encode proteins lacking transmembrane and catalytic domains of PTPRQ respectively (Goodyear et al., 2003). Cochlear development was normal in both mice and there was progressive deterioration of the sensory epithelium. Inner hair cells abnormalities were apparent by P1. Some stereocilia were misaligned or missing in the basal turn of cochlea. Stereocilia eventually fused and ultimately the organ of Corti disappeared in some mice by the age of three months (Goodyear et al., 2003).

SERPINB6 (DFNB91)

A single Turkish family has been described in which affected individuals have a mutation in *SERPINB6* segregating with hearing loss. The nonsense mutation, p.E245X was shown to substantially decrease the amount of the mutant transcript in blood of affected individuals (Sirmaci et al., 2010). The degree of hearing loss is moderate to severe with some residual hearing in all affected individuals. The 54 year old individual was the oldest and had the severest degree of hearing loss with greater degree of loss at high frequencies. The two younger individuals 24 and 23 years respectively, presented with moderate to severe hearing loss which was more severe in the 23 year old patient. Progressive nature of hearing loss was self reported by affected individuals but had not been documented by audiometry.

SERPINB6 is present in the hair cells in the organ of Corti as well as the greater epithelial ridge and may function as an inhibitor of proteases. It is hypothesized that SERPINB6 prevents non-specific tissue damage to inner ear tissue by inhibiting proteases. A transgenic mouse line lacking *Serpinb6* was created (Scarff et al., 2004) but the hearing status of the mice and inner ear structure was not evaluated. It will be interesting to identify if *Serpinb6*$^{-/-}$ mice have deafness at onset of hearing or whether they exhibit progressive deafness.

So far the results of genetic studies have revealed that although moderate to severe hearing loss is the usual finding for individuals with mutations in *STRC*, *TECTA* and *OTO* and in some individuals with mutations which cause progressive deafness, some individuals with mutations in other genes, for example *GJB2*, *CLDN14* or *TRIC* also have similarly milder phenotypes. Additionally, identical mutations in a gene may cause either progressive or stable hearing loss (Bashir et al. manuscript in preparation). Research has also shown that genes involved in progressive hearing loss may also have implications for age related hearing loss. For example, a polymorphism in *Cdh23* has been associated with age related hearing loss in different mice strains (Noben-Trauth, Zheng & Johnson, 2003).

2.4a Moderate to severe or progressive deafness in Usher Syndrome

Usher syndrome (USH) is a common syndrome of deafness-blindness and can be easily misdiagnosed as nonsyndromic hearing loss since onset of retinitis pigmentosa is gradual and the early manifestation can be very mild in some cases. So far mutations in 4 genes have been identified which cause the less severe phenotypes of hearing loss in Usher syndrome (*USH2A*, *GPR98*, *WHRN* and *CLRN1*). Additionally, some mutations of genes which cause Usher type 1 can also cause phenotypes termed as atypical usher syndromes.

Hearing loss for USH2 can vary from mild to severe in degree and may also show interfamilial variation (Abadie et al., 2011). The four Usher genes are expressed in hair cells where except for CLRN1, all proteins interact at the ankle link in the stereocilia and form a complex.

USH2A (USH2A)

Usher type 2A is the most frequent cause of Usher syndrome. A large number of missense, nonsense, insertion and deletion mutations have been identified in *USH2A*. The mutations were first described in North European, Spanish and African American patients (Eudy et al., 1998). *USH2A* encodes a large transmembrane protein, usherin, with an intracellular PDZ binding domain. Usherin is present in both outer and inner hair cells stereocilia and cannot be detected by 2 months of age in mice (Liu et al., 2007). *Ush2a*$^{-/-}$ transgenic mice have a moderate, non-progressive hearing loss which is more noticeable at high frequencies, mimicking the phenotype observed in humans (Liu et al., 2007). In the ears of the *Ush2a*$^{-/-}$ mice the inner hair cells and stereocilia are intact in all but at the basal turn of the cochlea where widespread loss of outer hair cells is observed.

GPR98 (USH2C)

Mutations of *GPR98* or *VLGR1* were first described in USH2 patients from United States and Sweden (Weston et al., 2004). *Gpr98* is expressed transiently during the first week in mice and is no longer detectable by P11. GPR98 forms the ankle links that connect the stereocilia of hair cells at their base in the developing hair cell bundles. Transgenic *Vlgr1/del7TM* mice which lack transmembrane and cytoplasmic domains of the protein are severely deaf by third week of life and lack ankle links (McGee et al., 2006). The stereocilia are arranged in a more rounded shape as compared to the "V" like pattern present in the wild type mice. A gradual loss of both type of hair cells and pillar cells is observed at the base of the cochlea (McGee et al., 2006).

WHRN (USH2D)

The description of *USH2D (WHRN)* is based on only two families from Germany and Portugal. The patients in the German family had mild to moderate hearing loss (Ebermann et al., 2007a) while the Portuguese family had variable degree of hearing loss with post lingual onset which was progressive in nature (Audo et al., 2011). In the German family two mutations in *WHRN* were detected in compound heterozygosity, involving a nonsense mutation in exon 1 and a splice site mutation in intron 2. The splice site mutation causes an in-frame skipping of the second exon and is predicted to result in production of an aberrant protein (Ebermann et al., 2007a). In the Portuguese family a deletion mutation was detected in exon 2 which is predicted to truncate the protein or mark the message for nonsense mediated decay (Audo et al., 2011). These mutations disrupt only the long isoform of WHRN.

Mice with a targeted deletion of the long isoform of whirlin have some partial hearing (75 dB SPL) which is non-progressive in nature (Yang et al., 2010) . The inner hair cells stereocilia are unaffected while the outer hair cells stereocilia loose their characteristic "V" shaped formation and assume a "U" shape. Some of the stereocilia are missing from the innermost row in outer hair cells. However, unlike *whirler* mutant mice who are deaf due to a deletion in *Whrn* disrupting both isoforms of the protein, mice with targeted ablation of the long isoform of whirlin do not have abnormally short stereocilia.

CLRN1 (USH3A)

The deafness phenotype associated with USH3 involves postlingual, progressive hearing loss. The time of onset and severity of hearing loss can be highly variable (Ness et al., 2003). So far only one gene, *CLRN1* has been identified which causes an USH3 phenotype (Joensuu et al., 2001). In contrast to other world populations, mutations in *CLRN1* are a frequent cause of Usher syndrome in the Finnish population. *Clrn1*$^{-/-}$ mice have early onset hearing loss and are profoundly deaf by P30 (Geng et al., 2009). *Clrn1*$^{-/-}$ mice have demonstrated that CLRN1 is important for normal maturation of hair cells as well as the afferent nerve synapses. Absence of CLRN1 in mice leads to gradual loss of outer hair cells and supporting cells which is most severe at the basal turn of the cochlea (Geng et al., 2009).

CLRN1 is a small 232 amino acid transmembrane protein which is present at both the basal and apical poles of the hair cells with expression being higher in outer hair cells as compared to the inner hair cells (Geng et al., 2009; Zallocchi et al., 2009). *Clrn1* is also expressed in the spiral ganglion (Geng et al., 2009; Zallocchi et al., 2009). In mice, CLRN1 cannot be detected at the apex of hair cells at P1 and continues to be expressed in both the pre- and post-synaptic regions of outer hair cell type I afferent ribbon synapses (Zallocchi et al., 2009). Additionally, CLRN1 may also have a role in actin assembly (Tian et al., 2009) and intracellular vesicle transport (Zallocchi et al., 2009).

2.4b Atypical manifestations of hearing loss in Usher syndrome

Atypical USH is genetically heterogeneous. Two different mutations of *SANS* (*USH1G*) have been reported to cause a USH2 like phenotype in two consanguineous families from Turkey and Pakistan (Bashir, Fatima & Naz, 2010a; Kalay et al., 2005). Similarly, some mutations in *MYO7A* (*USH1B*) cause an USH3 phenotype (Liu et al., 1998). Additionally, two mutations in *CDH23* (*USH1D*), result in an atypical phenotype of milder USH3. These involve a missense and an intronic mutation which are compound heterozygous in a German family with two affected siblings (Astuto et al., 2002). Some USH2A mutations also cause atypical manifestations and the phenotype resembles that of USH3 (Liu et al., 1999). On the converse, it is interesting to note that though majority of the mutations in CLRN1 cause a USH3 phenotype, some mutations in the same gene cause a more severe USH1 phenotype (Aller et al., 2004; Pennings et al., 2003) or in some cases an USH2 phenotype (Sadeghi et al., 2005). The finding of identical mutations in some cases which cause both the less severe or the more profound USH phenotype suggest the importance of genetic background in manifestation of the disorder and a role of modifiers in its aetiology.

2.5 Modifiers in less severe hearing loss

To date a single modifier, *DFNM1*, has been mapped to chromosome 1 which completely ameliorates hearing loss (Riazuddin et al., 2000) but the gene is currently unknown. Targeted sequencing of the linked region from DNA of both affected and unaffected individuals using massively parallel sequencing technology may identify the causative change in future.

A role of modifier genes in reducing severity of hearing loss is suspected for many other deafness loci as well, especially those showing a wide phenotypic variation in presence of identical genetic mutations. However, currently no locus has been mapped or any gene identified as a potential modifier. Usually each family has few individuals with sufficiently different phenotypes to make gene mapping studies feasible. Using whole genome sequencing approaches in either a small subset of such individuals or in larger families may identify genetic modifiers in future.

GJB2 is the most widely sequenced deafness genes and mutations in this gene are associated with deafness which is mild in degree to more profound losses. However, it has not been possible to map a genetic modifier which reduces severity of hearing loss using either traditional linkage analysis or association studies. A whole genome association study on DNA of more than a thousand *GJB2* c.35delG homozygous individuals living across Europe and North America regions failed to identify a single locus as a modifier in individuals with mild phenotypes of hearing loss. However, some SNPs with smaller modifying effects on the phenotype were identified (Hilgert et al., 2009). It is possible that a more stringent ethnic definition and data re-analysis in a smaller group may succeed in mapping a single locus for at least a subset of the participants.

The unavailability of different cell types derived from inner ear tissues in humans have inhibited direct evaluation of modifier genes in hearing loss by transcriptional analysis as for other disorders such as spinal muscular atrophy (Oprea et al., 2008). However, induced pluripotent stem cell lines can be derived from more and less severely affected deaf individuals respectively. These could be then differentiated *in vitro* into the relevant cochlear cell types followed by comparison of their mRNA expression profiles. This may help in identification of genetic modifiers in future.

Modifiers of hearing loss identified in mice may also be eventually found to be implicated in humans. Currently, only two genes have been identified which result in complete rescue of hearing defects in mice. For example alleles of *Cdh23* and *Mtap1a* can rescue hearing loss in mice with mutations in *Atp2b2* and *Tub* respectively (reviewed by Yan & Liu, 2010). Targeted sequencing of these genes in humans may also identify comparable variants important for modification of hearing loss.

3. Conclusions

Genes and loci continue to be identified in aetiology of moderate to severe and progressive deafness. Current research has revealed that different alleles of a deafness gene can cause less severe hearing loss or more profound deafness. Further work needs to be carried out to identify additional loci and genes for progressive deafness and those for less severe hearing loss phenotypes as well as modifiers in the genetic background that suppress or enhance hearing loss. The contribution of different genes to moderate to severe and progressive hearing loss also needs to be studied in different world populations. Additionally, it remains important to document hearing loss in families which have already been described to suffer from moderate to severe hearing loss in order to check for progression of hearing loss in future. Strategies need to be evolved for identification of modifiers which will elucidate molecular pathways involved in normal hearing. This may be of help in designing strategies to treat and cure deafness in future.

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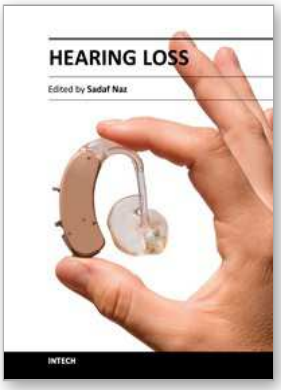

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Authored by 17 international researchers and research teams, the book provides up-to-date insights on topics in five different research areas related to normal hearing and deafness. Techniques for assessment of hearing and the appropriateness of the Mongolian gerbil as a model for age-dependent hearing loss in humans are presented. Parental attitudes to childhood deafness and role of early intervention for better treatment of hearing loss are also discussed. Comprehensive details are provided on the role of different environmental insults including injuries in causing deafness. Additionally, many genes involved in hearing loss are reviewed and the genetics of recessively inherited moderate to severe and progressive deafness is covered for the first time. The book also details established and evolving therapies for treatment of deafness.

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